Interval Carcinomas in the European Randomized Study of Screening for Prostate Cancer (ERSPC)–Rotterdam

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Background: **The interval cancer rate is an important parameter for determining the sensitivity of a screening procedure and the screening interval. We evaluated the time and mechanism of detection and the stage distribution of interval prostate cancers diagnosed during a 4-year screening interval.** ***Methods:*** **We determined the rate of interval cancers and the sensitivity of the screening protocol (involving prostate-specific antigen, digital rectal and transrectal ultrasound examinations) in a cohort of 17 226 men (8350 on the screened arm, 8876 on the control arm) enrolled consecutively on the European Randomized Study of Screening for Prostate Cancer–Rotterdam. Men on the screened arm received a first screen between October 1993 and December 1996 and a scheduled second screen 4 years later. Prostate cancers detected in men enrolled on the control arm over the same 4-year period and, between screens, in men on the screened arm, were identified by linkage to the Dutch national cancer registry.** ***Results:*** **During the first screen, 412 prostate cancers were detected. During the subsequent 4-year period, 135 cancers were diagnosed in men in the control arm and 25 cancers were diagnosed in men in the screened arm. Seven of the 25 cancers were diagnosed in men who had refused a recommended biopsy at their initial screen. Of the remaining 18 cancers, all were classified as stage T1A–C or T2A and none were poorly differentiated or metastatic. The rate of interval cancers relative to the number of cancers in the control group was 18.5% (25/135), or 13.3% (18/135), if the seven who refused an initial biopsy were excluded. The sensitivity of the screening protocol was 79.8% when considering all 25 interval cancers and 85.5% when considering 18 interval cancers.** ***Conclusion:*** **The interval cancer rate with a 4-year screening interval was low, confirming that the screening procedure has a high sensitivity and that the 4-year screening interval is reasonable. [J Natl Cancer Inst 2003;95:1462–6]**

The quality and effectiveness of a cancer screening program cannot be evaluated on the basis of results from the initial screening round. Instead, these properties must be evaluated with consideration for crucial indicators, such as detection rates from subsequent screening rounds, interval cancer rates, underlying cancer incidence, and tumor characteristics.

It will be several years before the outcomes, including effects on cancer-related mortality, of population-based, randomized screening trials—such as the European Randomized Study of Screening for Prostate Cancer (ERSPC) *(1)* and the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) *(2)*—will be available. In the meantime, intermediate endpoint analyses are important indicators for the quality of the screening procedures. One such intermediate endpoint for prostate cancer screening is the rate of interval cancers, i.e., cancers detected in the screened population between screening rounds and outside screening trials. Because the rate of interval cancers reflects the number of and the time needed for new cancers to surface clinically, it is an important parameter for determining the sensitivity of the screening procedure and the proper screening interval. The sensitivity of the screening procedure in the ERSPC, which included collection of sextant biopsy specimens, was estimated to be approximately 70% *(3,4)*. In this study, we evaluated the time and mechanism of detection and the stage distribution of prostate cancers diagnosed during a 4-year screening interval in a subgroup of the ERSPC study population.

Patients and Methods

Patients

We studied a cohort of 17 226 men aged 55–74 years (8350 men in the intervention arm and 8876 men in the control arm) (Fig. 1) enrolled on the ERSPC–Rotterdam. All men in the intervention arm had their first screen between October 1993 and December 1996. ERSPC–Rotterdam uses a 4-year screening interval. The second screen was completed by the end of December 2000. This allowed a full 4-year period for the study of interval cancers. All men in the control arm were enrolled simultaneously.

At the first screen, all participants in the intervention arm were offered a prostate-specific antigen (PSA) level measurement, digital rectal examination (DRE), and transrectal ultrasound (TRUS) examination. Individuals who had PSA levels equal to or higher than 4.0 ng/mL or who had PSA levels of 0–3.9 ng/mL and suspicious DRE and/or TRUS results were then recommended to have lateral sextant transrectal biopsies, as stated for the Rotterdam screening regimen. All participants received extensive information about potential benefits and harms of screening for prostate cancer as part of the informed consent procedure.

To identify individuals with prostate cancer in each study arm, including interval carcinomas in individuals in the intervention arm, a database from the local Rotterdam Comprehensive Cancer Registry was checked annually. For men diagnosed with prostate cancer and those known to have died from other causes, data regarding the diagnosis of prostate cancer were collected and entered into the ERSPC database. All data regarding prostate cancer staging and management were obtained by reviewing the patients' medical records at the regional hospitals.

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See "Note" following "References."

DOI: 10.1093/jnci/djg057

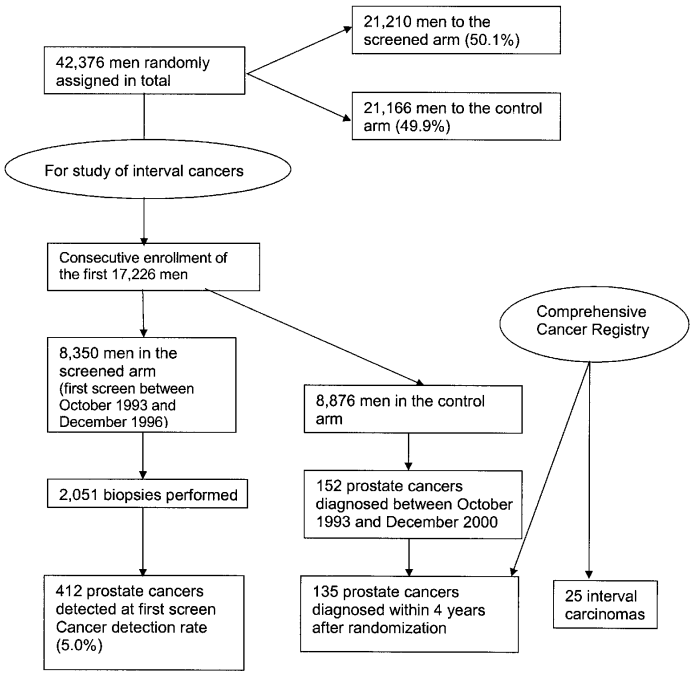

Fig. 1. ERSPC–Rotterdam consort diagram relating to interval cancers.

For individuals identified with interval carcinomas, histologic slides of sections of prostate cancer biopsy specimens were retrieved from the pathologic storage facilities of the local hospitals. All diagnoses and Gleason scores abstracted from the patients' medical records were reviewed by one of the authors (T. H. van der Kwast). If discrepancies occurred among the diagnoses and Gleason scores from the patients' medical records and those assigned after review, blinded re-grading by the reference pathologies was used. The pathologic features of the cancers, including the extent of the cancers and Gleason scores, in men who had undergone radical prostatectomy were obtained in the same way as those of the biopsy specimens to collect a maximum amount of reliable prognostic information. All tumors were staged according to the 1992 Tumor–Node–Metastasis (TNM) System *(5)*. All men diagnosed with prostate cancer, regardless of study arm, received standard medical care, which meant that the evaluation of symptoms and diagnosis and management of the prostate cancer were provided by local urologists not associated with the study. The study was approved by the Minister of Health of The Netherlands (via letters dated 15 August 1997 and 05 February 2001 from Dr. E. Borst-Eilers, The Hague). Written informed consent was obtained from each participant.

Statistical Analysis

The rate of interval cancers was calculated as the ratio of the number of interval cancers to the number of cancers found in the control group during the same time period. Sensitivity was calculated according to the proportional incidence method *(6)*.

Results

The ERSPC–Rotterdam recruited 42 376 participants and randomly assigned them to either the intervention arm (21 210 men) or the control arm (21 166 men) (Fig. 1). For the purpose of this study, we used a cohort of 17 226 men (8350 in the intervention arm and 8876 in the control arm) who were consecutively enrolled on the ERSPC–Rotterdam. Men in the intervention arm had their first screen between October 1993 and December 1996. At the end of December 2000, all participants in the intervention arm had been followed to the completion of their scheduled second screen, a 4-year follow-up period.

Of the 152 prostate cancers diagnosed among individuals in the control arm, 135 were diagnosed within 4 years of randomization. Among individuals in the intervention arm, 25 prostate cancers were not diagnosed as a result of screening but were diagnosed outside the trial and within 4 years of randomization. The prognostic characteristics of the 25 cancers are described in Tables 1–4. Twenty-two of the 25 cancers were classified as early-stage (T1A, T1B, T1C, or T2A). None of the cancers were poorly differentiated or metastatic (N+ or M+).

Of the 25 cancers, seven were diagnosed among men who had a biopsy indication initially but who refused a recommended biopsy at the initial screen. Three of the seven cancers were advanced cancers, with a T3 or worse tumor stage. None of these seven men had metastatic disease. Five of the seven cancers were detected within 1 year of the initial screening examination (Table 1).

Of the remaining 18 men diagnosed with an interval prostate cancer, four were aged 75 years or older. In three of the four men, the cancers were carcinomas diagnosed by transurethral

Table 1. Tumor characteristics of interval cancers among men enrolled in the European Randomized Study of Screening for Prostate Cancer–Rotterdam who refused a recommended biopsy at the initial screen and their therapy choices (n = 7)*

Initial screen						Diagnosis and treatment						
Patient	PSA, ng/mL	DRE	TRUS	Biopsy	Interval, mo†	Age, y	PSA, ng/mL	T stage‡	Gleason score for biopsy specimen	Therapy	pT stage‡	Gleason score for RP tissue specimen
1	6.6	B	B	N	44	62	8.8	T1C	6	Radical prostatectomy	PT2C	5
2	7.1	B	B	N	25	67	9.6	T1C	6	Radiotherapy	—	—
3	16.0	—	—	N	8	73	18.7	T1C	8	Radiotherapy	—	—
4	21.0	—	—	N	0	61	21.0	T1C	7	Radical prostatectomy	PT2A	6
5	62	T2C	T2C	N	5	71	65.0	T3A	9	Radiotherapy	—	—
6	2.8	T2C	B	N	3	68	2.8	T3B	6	Radiotherapy	—	—
7	19.1	—	—	N	4	72	19.1	T4	7	Endocrine therapy	—	—

*PSA = prostate-specific antigen; DRE = digital rectal examination; TRUS = transrectal ultrasound examination; RP = radical prostatectomy; B = benign; N = not done (refused).

†Interval refers to the number of months between the first screen and a prostate cancer diagnosis.

‡T stage and pT stage represent tumor extent determined before and after excision of the prostate. All tumors were staged according to the Tumor–Node–Metastasis System of 1992 *(5)*. No lymph nodal or distant metastases were found.

resection of the prostate (TURP), which was done for what was thought to be benign disease. These three cancers are considered incidental cancers (Table 2). The remaining 14 cancers were diagnosed clinically, as indicated in Tables 3 and 4. Five of the cancers were diagnosed by cystoprostatectomy for bladder cancer, and two were diagnosed by TURP for benign disease. The other seven cancers were diagnosed because of increasing PSA levels or complaints of prostatism.

During the initial screen, 412 prostate cancers were diagnosed. Thus, the proportion of interval cancers among all cancers diagnosed in men in the screening arm was 6.1% (25/412). The proportion of interval cancers in men in the screened arm, relative to cancers diagnosed in men in the control arm during the 4-year period after randomization was 18.5% (25/135). If the seven men who refused a biopsy after their initial screen are not included among the interval cancers, then the proportion of interval cancers relative to the control arm would be 13.3% (18/135). Other definitions of interval cancer rates can easily be applied using the information provided in the tables.

The incidence of prostate cancer was 21 per 1000 person-years among men in the screened arm and 3.9 per 1000 person-years among men in the control arm. The number of screen-negative men in our cohort is 7938, which represents men who actually had a negative screen (7798), men from whom a biopsy specimen could not be taken because they used anticoagulants (48), and men who were non-attenders (92). The expected number of cancers in the screen-negative men would be 123.8 (7938 × 3.9/1000 × 4 years of follow-up). Sensitivity was calculated according to the proportional incidence method *(6)* and was estimated to be 79.8% (123.8 – 25/123.8). If the seven men who refused a biopsy during the first screen were not considered among the interval cancers, then the sensitivity was estimated to be 85.5%.

DISCUSSION

This is the first report on interval carcinomas in prostate cancer screening from the ERSPC. The rate of interval cancers was low and reflects the usefulness of a screening interval of at least 4 years. In general, cancers not detected in the initial screening visit may be detected as interval cancers, may be detected in the second screening round, or may remain occult during the lifetime of their carriers. The occurrence of interval carcinomas may be the result of a lack of sensitivity of the screening test or of an interscreening interval that is too long. Increased sensitivity (and a lower proportion of interval cancers) can be reached with more aggressive screening strategies, but such an approach would increase the rate of overdiagnosis, a problem that is inherent in screening for prostate cancer.

Characterization of Interval Cancers

In our study, interval cancers were defined as prostate cancers detected during 4 years after randomization in the screened population but outside the screening protocol. Because the first screening round is complete only if men who are recommended to have a biopsy did in fact do so, the cancers found in the seven patients listed in Table 1 who refused to have a prostate biopsy may not represent true interval cancers. The information regarding classification of the interval cancers in the tables is purely descriptive and does not contain any judgments on what may be a clinically relevant or irrelevant cancer. Some cancers are diagnosed as so-called "incidental prostate cancers" (i.e., T1A and T1B cancers). Their high prevalence of approximately 30% at autopsy is well established in men aged 50–60 years *(7)*. Some incidental prostate cancers were found during treatment for other diseases, such as during cystoprostatectomy for bladder cancer (cases 12–16) and during transurethral resection for obstructive benign prostatic hyperplasia (cases 17 and 18). Four cases (11, 19, 20, and 21), all stage T1C, were found through opportunistic screening. By definition, a T1C cancer can be diagnosed only on the basis of an elevated PSA level.

Potential Biases

It is unclear why interval cancers are rarely mentioned in the prostate cancer screening literature. One reason may be that interval cancers do not occur because of the short intervals that are in general use (6–12 months) and are recommended in the United States *(8)*. ERSPC chose a 4-year screening interval in light of the limited evidence available regarding lead time in prostate cancer *(9–11)* during the ERSPC protocol development phase (1992 through 1994). The Swedish center of ERSPC uses a screening interval of 2 years and has described nine interval cancers that were found over a 4-year period *(12)*. Their data cannot be compared with ours because the difference in screening intervals will bias the determination of rates of interval cancers.

Several factors could have influenced the results of this study by either raising or lowering the number of interval cancers or their rate relative to prostate cancer incidence in the control group. These factors include the frequency of screening, the screening procedures used, the age group screened, and the un-

Table 2. Tumor characteristics of interval cancers detected among men enrolled in the European Randomized Study of Screening for Prostate Cancer–Rotterdam who were not eligible for rescreening because of age (older than 75 years) and their therapy choices (n = 4)*

Initial screen					Diagnosis and treatment					
Patient	PSA, ng/mL	DRE	TRUS	Biopsy (histology)	Interval, mo†	Age, y	PSA, ng/mL	T stage‡	TURP/Gleason score for biopsy specimen	Therapy
8	1.4	B	B	N	44	76	1.0	T1A		Watchful waiting
9	2.8	B	T2	Y (chronic prostatitis)	46	78	3.2	T1B	4	Watchful waiting
10	4.0	B	B	Y (no malignancy)	33	76	6.0	T1B	4	Watchful waiting
11	2.4	B	B	N	48	77	5.3	T1C	6	Radiotherapy

*PSA = prostate-specific antigen; DRE = digital rectal examination; TRUS = transrectal ultrasound examination; TURP = transurethral resection of the prostate (for apparently benign disease); B = benign; N = not done; Y = yes, biopsy performed.

†Interval refers to the number of months between the first screen and a prostate cancer diagnosis.

‡T stage = tumor extent determined before and after excision of the prostate. All tumors were staged to the Tumor–Node–Metastasis System of 1992 *(5)*. No lymph nodal or distant metastases were found.

Table 3. Tumor characteristics of interval cancers detected among men enrolled in the European Randomized Study of Screening for Prostate Cancer–Rotterdam who were diagnosed with cancer by cystoprostatectomy or transurethral resection of the prostate (TURP; for apparently benign disease) and their therapy choices (n = 7)*

Initial screen					Diagnosis and treatment						
Patient	PSA, ng/mL	DRE	TRUS	Biopsy (histology)	Interval, mo†	Age, y	PSA, ng/mL	T stage‡	Therapy	pT stage‡	RCP/TURP Gleason score
12	1.6	B	B	N	43	74	—	—	Cystoprostatectomy	PT2C	7
13	1.7	B	B	N	38	73	2.4	—	Cystoprostatectomy	PT2A	4
14	1.8	B	B	N	10	65	2.4	—	Cystoprostatectomy	PT3A	5
15	1.8	B	B	N	32	70	2.5	—	Cystoprostatectomy	PT2A	6
16	7.2	B	B	Y (hyperplasia)	10	71	8.0	—	Cystoprostatectomy	PTX	6
17	2.2	T2A	T2A	Y (no malignancy)	4	67	3.1	T1A	Watchful waiting	—	5
18	4.9	B	B	Y (no malignancy)	28	68	6.0	T1B	Watchful waiting	—	3

*PSA = prostate-specific antigen; DRE = digital rectal examination; TRUS = transrectal ultrasound examination; RCP = radical cystoprostatectomy; B = benign; N = not done; Y = yes, biopsy performed.

†Interval refers to the number of months between the first screen and a prostate cancer diagnosis.

‡T stage and pT stage = tumor extent determined before and after excision of the prostate. All tumors were staged according to the Tumor–Node–Metastasis System of 1992 *(5)*. No lymph nodal or distant metastases were found.

Table 4. Tumor characteristics of interval cancers detected among men enrolled in the European Randomized Study of Screening for Prostate Cancer–Rotterdam who were clinically diagnosed with cancer and their therapy choices (n = 7)*

Initial screen					Diagnosis and treatment							
Patient	PSA, ng/mL	DRE	TRUS	Biopsy (histology)	Interval, mo†	Age, y	PSA, ng/mL	T stage‡	Gleason score for biopsy specimen	Therapy	pT stage‡	Gleason score for RP tissue specimen
19	3.0	B	B	N	26	63	5.3	T1C	6	Watchful waiting		
20	3.6	B	B	N	30	68	5.4	T1C	6	Watchful waiting		
21	2.6	B	B	N	26	73	6.4	T1C	6	Radiotherapy		
22	3.0	B	B	N	31	74	5.3	T2A	7	Radiotherapy		
23	3.4	B	B	N	28	72	6.9	T2A	6	Radiotherapy		
24	18.2	B	B	Y (prostatitis)	21	67	15.4	T2A	7	Radical prostatectomy	PT3a	6
25	20.2	T2C	T2A	Y (no malignancy)	28	69	25.0	T2A	6	Radical prostatectomy	pT2A	6

*PSA = prostate-specific antigen; DRE = digital rectal examination; TRUS = transrectal ultrasound examination; RP = radical prostatectomy; B = benign; N = not done; Y = yes, biopsy performed.

†Interval refers to the number of months between the first screen and a prostate cancer diagnosis.

‡T stage and pT stage = tumor extent determined before and after excision of the prostate. All tumors were staged according to the Tumor–Node–Metastasis System of 1992 *(5)*. No lymph nodal or distant metastases were found.

derlying incidence. It is well known that collecting more biopsy specimens will detect more cancer *(13–15)*. This knowledge has led to a change in clinical practice in several ERSPC countries but not in The Netherlands. However, 49 cancers were detected at temporary early rescreens performed on men in ERSPC–Rotterdam who had a negative biopsy during the first screening round *(16)*. These cancers are part of the first round detection rate and therefore are likely to have decreased the number of interval cancers.

The prevalence of opportunistic screening, defined as screening of participants outside the study, in the intervention and the control arms could be another important source of bias. Opportunistic screening was therefore subject to continuous monitoring. The preliminary results of opportunistic screening in the ERSPC have been published *(17,18)*. The data show that effective screening, which involved a PSA test combined with a biopsy according to indication, occurred in about 10% of men in the control arm over a 4-year period *(18)*. The proportion of men who were classified as T1C and, by definition, were diagnosed by PSA-driven screening is presently under investigation.

Our results could also be biased by incomplete incidence data obtained from the cancer registry. However, all Dutch cancer registries are maintained according to one countrywide protocol; one regional comprehensive cancer center that follows the protocol evaluated the completeness of cancer registration and found that 96.2% of the eligible malignancies were included in the registry *(19)*. Thus, it is reasonable to expect that the completeness of the data obtained from the Rotterdam Cancer Registry is similar. ERSPC procedures include a double check of the incidence data obtained from the registry. This additional check has rarely led to corrections of the cancer registry database.

Lead Time

Lead time is an important codeterminant of the sensitivity of a screening procedure. Determinations of lead time *(9–11)* were made on the basis of clinical diagnoses of prostate cancer associated with archived serum samples used during follow-up periods of 10–15 years. Gann et al. *(11)* point out that lead time is not a parameter that depends exclusively on test characteristics but a parameter that depends also on prognostic factors such as stage at the time of diagnosis, tumor aggressiveness, patient age, and other disease-related factors. Factors associated with a worse outcome are likely to be associated with a shorter lead time than those associated with clinical cancers. The ERSPC has made two attempts to model lead time. Auvinen et al. *(20)* estimated a lead time of 5–7 years on the basis of the duration of

follow-up that was needed to accrue the same expected number of incident prostate cancer cases in the absence of screening as were detected in the initial screening round. These estimates vary from those found by Draisma et al. *(21)* who, using the MISCAN technique, found that for a group of men aged 55–75 years and a screening interval of 4 years, lead time was 10.3 years (range = 9.9–11.2 years). Lead times were age-dependent *(21)*. This information also confirms the choice of a long screening interval in the ERSPC.

Sensitivity of PSA-based screening was estimated by Hakama et al. *(22),* who used follow-up and PSA determinations from archived serum samples. They studied 21 387 men in whom 104 prostate cancers were detected clinically. The sensitivity of the PSA test was 86% for cancers that were diagnosed within 5 years of collecting the blood sample. This estimate is in line with our sensitivity results of 79.8%–85.5%. However, it should be noted that we used PSA, DRE, and TRUS in our screening protocol.

Clinical Importance of Interval Cancers

If we had detected a large number of interval cancers and/or interval cancers with advanced stage or otherwise poor prognostic factors, it would have indicated that the screening protocol had a low sensitivity. However, all interval cancers were detected at a locally confined stage, and only three had an unfavorable Gleason score of 7, one in Table 3 and two in Table 4, not counting those in Table 1 (these are the case patients who refused biopsy). The preponderance of low Gleason scores is in line with the fact that many of the cancers were detected by transurethral resection for benign prostatic hyperplasia and as incidental findings of cystoprostatectomy. T stage and Gleason score have poor intra- and interobserver reproducibility and poor correlation with definitive findings in radical prostatectomy specimens and often result in understaging. Future screening tests and screening intervals will have to consider these difficulties and aim to identify aggressive cancers in time for curative management.

Conclusion

The rate of interval cancers found within ERSPC–Rotterdam with a 4-year screening period was exceedingly low. The interval cancers were associated with favorable prognostic factors. The data confirm a high sensitivity of the screening procedure and the usefulness of a 4-year screening interval. The resulting estimates of lead time are in agreement with the findings of others *(9–11,21)* and with the long natural history of the disease. The results confirm that very few, if any, aggressive prostate cancers escape screening with the procedures used within the ERSPC.

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Note

Manuscript received March 18, 2003; revised July 17, 2003; accepted July 25, 2003.